REMARKS

As an initial matter, Applicants gratefully acknowledge withdrawal of several claim rejections under 35 USC §112, second paragraph. Office Action at pgs. 2-3.

Support for the claim amendments can be found throughout the instant application including the Drawings and claims as filed originally.

Claim 1 has been amended so that the variable region must include a specified CDR of the heavy and light chains. Specific support for the amendment can be found in claim 18 as filed originally (in which the humanized monoclonal antibody features a variable region that includes at least part of the sequence in Figure 6). Further support is apparent from originally filed claim 20 (showing the heavy and light chain CDRs as discreet units) and claim 20 (claiming at least part of the Figure 6 sequences). Still further support can be found at pg. 9, 3rd paragraph, in which Applicants report that the invention includes modifications such as deletions of featured variable regions.

Particular support for "modification" in claim 1 can be found at pg. 9 for instant (disclosing, among other things, that variable region modifications do not diminish binding).

Claim 20 has been amended with language from claim 32. Claims 23, 29, 39 and 40 have been amended to improve claim clarity.

No new matter has been added by virtue of the claim amendments.

Turning to the Office Action, claim 41 stands rejected under obviousness-type double patenting as being unpatentable over claim 9 of U.S Pat. No. 5,747,272. The rejection will be addressed once there is indication of allowable subject matter.

Claims 1, 2, 14, 17-20, 29, 32-40, 43-44 stand rejected under 35 USC §112, first paragraph, as not being enabled for humanized antibodies containing at least part of a human

immunoglobulin constant region and said murine variable region contains at least part of a murine immunoglobulin variable region as shown in Figure 3 (SEQ ID NO: 21) or Figure 6 (SEQ ID NO: 42). Action at pgs. 3-4. While Applicants respectfully disagree with the rejection, basis for it has been addressed by this submission.

In particular, the variable regions have been more specifically defined to include at least one specifically defined CDR from the light and heavy chains. Thus, the PTO's concern that the claimed antibody might include a variable region having **one amino acid** in common with sequence shown in Figures 3 or 6 has been mooted. As written, the antibody of claim 1 must feature the specified CDR sequences.

Moreover, the claim 1 (even as unamended) includes functional language the requires the claimed antibody to bind antigen. As one working in this field would appreciate, such an antibody cannot have a variable region with just one amino acid. Such an antibody, even if constructed, would be understood to be incapable of binding antigen in any productive way.

On this ground alone, it is respectfully submitted that the rejection has been addressed and should be withdrawn.

Applicants respectfully disagree with the assertion that one of skill in possession of the instant specification would accept "the unpredictability in determining acceptable sequence variations". Action at pg. 4. That is simply not accurate.

In this respect, the instant specification shows how to make, use and test a variety of suitable variable region sequences including those now featured in claim 1.

For instance, Fig. 1 provides a general cloning strategy for obtaining variable gene fragments of both the 11E10 and 13C4 antibodies. Useful oligonucleotides for performing the strategy are given in Figs and 2 and 5. A complete DNA and amino acid sequence for the 13C4 (Fig. 3) and 11E10 (Fig. 6) antibodies has been provided. Fig. 4 presents a general

strategy for making vectors that include variable regions of the 13C4 antibody. See also Fig. 7 which shows, among other things, how to make vectors with 11E10 antibody variable regions.

Such general guidance is supported by more detailed disclosure in the specification.

For instance, at pg. 9, the Applicant reported that his invention should not be limited to any particular variable region. Modifications thereof (deletions, additions, and substitutions) were contemplated provided they "do not appreciably diminish the characteristic binding associated with the exemplified variable regions". Specification at pg. 9.

The specification identified the CDRs (complimentarity determining regions) of the 13C4 (Fig. 3) and 11E10 (Fig. 6) antibodies, thereby defining a key variable domain structure by sequence.

Further the specification shows how to use particular cloning methods and unique oligonucleotides to isolate the variable region of the 13C4 (Example 1) and 11E10 (Example 4). Methods for testing for functional variable regions are also provided as ELISA (Examples 3, 6). The specification provides further testing protocols including a Vero cell cytotoxity assay and antisera neutralization assay (Example 7); as well as a passive immunization testing method (Example 8).

Accordingly, and in view of the detailed disclosure provided herein, it is submitted that whatever manipulations are needed to make and use the invention of claim 1 (as amended), they are not undue and certainly well within the standards set forth by the Federal Circuit. See *In re Wands* 858 F.2d 731 (Fed. Cir. 1988).

In view thereof, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 23, 29 and 39-40 stand rejected under 35 USC §112, first paragraph, on several grounds including "no evidence has been provided that illustrates or even suggests that the claimed pharmaceutical compositions are capable of eliciting a beneficial therapeutic response..." Applicants respectfully disagree.

To the extent the evidence requested by the Office is even needed to satisfy the requirements of 35 USC §112, first paragraph, the rejection has been mooted by amendment. More precisely, claims 23, 29, 39 and 40 now recite "composition" instead of "pharmaceutical composition".

Remaining bases for rejection of claims 23, 29 and 39-40 have been addressed as discussed above.

In view thereof, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 2, 13-20, 23, 29 and 32-41 stand rejected as being obvious over the Spiers reference, the O'Brien patent, in view of a PCT application by Carter et al. Applicants respectfully disagree with the rejection for reasons of record and as follows.

The Office has taken the position that one of skill could use methods taught by Carter to make the antibodies provided by Spiers and O'Brien as cited. It is also pointed out by the Action that **"standard sequence methodologies"** could be used to obtain the sequences of the 11E10 and 13C4 antibodies. However, no reference is cited that discloses what a standard sequence methodology is or how a worker would be motivated to use it to combine the cited references in the way suggested by the Office.

Respectfully, the rejection is improper. As the Federal Circuit has made clear it is improper to base an obviousness rejection on subjective belief and unknown authority. In re Lee, 277 F.3d 1338; 61 USPQ 2d (BNA) 1430.

As understood, *Lee* involved a situation in which the Board relied on its "general knowledge to negate patentability." *In re Lee*, 277 F.3d at 1345. In such circumstances, the Court held that such "knowledge must be articulated and placed on the record." Id. The Court further explained "that 'deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is 'basic knowledge' or 'common sense.'" Id. At 1344, 61 USPQ2d at 1434-35 (quoting *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001)).

Like *Lee*, the Office is relying on its "general knowledge to negate patentability" of the present invention. That is, it is presuming without any objective evidence on the record that the sequencing methodologies referenced in the Action are standard and that a worker would know to use them in the way suggested by the PTO in view of Spiers, Carter, and O'Brien. On this basis alone, the rejection is improper. A motivation to combine cannot be resolved on subjective belief and unknown authority. In re Lee, *supra*.

Even if the Office were to determine that instant §103 rejection is somehow proper, it fails to withstand scrutiny on other grounds.

First, and as the Declaration by Dr. Hing Wong makes clear, a worker would be particularly dissuaded from isolating the sequence of the 13C4 and 11E10 murine antibodies. The Approach suggested by the Examiner would not work according to Dr. Wong. Decl. at ¶ 9.

Dr. Wong stated in detail why it would be difficult or impossible to isolate variable regions using the approach urged by the Examiner. Decl. at ¶¶ 10-11.

Instead of the approach suggested by the Office, Dr. Wong stated how he isolated nucleic acid encoding the 13C4 and 11E10 antibodies after considerable effort. Decl. at ¶¶ 11-18.

According to the Office, "Dr. Wong's arguments are predicated on the mistaken belief that the Examiner implied that the cloning approach described by Carter could be used to obtain the sequences of the 11E10 and 13C4 antibodies". Action at 8. Respectfully, that is not correct. If anything, Dr. Wong and his co-inventors identified, understood, and avoided the problems inherent in the Examiner's suggested cloning approach. Decl. at ¶ 19. Neither the problem nor the cloning solution discovered by Dr. Wong and his co-inventors is taught or even suggested by the PTO's combination of references.

It is noted that the Office has merely repeated certain statements made by Dr. Wong without sufficient comment or explanation why the evidence therein is insufficient to overcome the obviousness rejection §103. Respectfully, this is an improper basis for reviewing the Declaration. See MPEP 716.01 (reporting criteria for reviewing Rule 131 Declarations).

On this basis alone, it is submitted that the obviousness rejection should be reconsidered and withdrawn.

Applicants respectfully disagree with the rejection on further grounds.

As pointed out by Dr. Wong throughout his Declaration, it was certainly not obvious to make the claimed antibodies. Nothing in the cited references, teaches, suggests or provides any motivation to make those antibodies. At best, the Office has used an "obvious to try" standard that has been expressly rejected by the Federal Circuit. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (the cited art must suggest the invention and provide a reasonable expectation of success). As cited above, there is

no suggestion in the cited references to make the invention. Moreover, and in few of the many pitfalls identified by Dr. Wong in his Declaration, there would be no reasonable expectation of success to make that invention in view of the method suggested by the USPTO.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Although it is not believed that any additional fee is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. **04-1105** should any fee be deemed necessary.

Respectfully submitted,

Date: March 22, 2004

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Doc.438367